Case Studies: Models for Establishing Clinically Relevant Drug Product Specifications

Sandra Suarez Sharp, Ph. D.

Office of New Drug Quality Assessment/Biopharmaceutics

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Disclaimer

- In this presentation I am relying on personal observation and opinion. This presentation is not intended to convey official US FDA policy, and the comments are not binding on the US FDA or the regulated industry

Outline

- Clinically Relevant Drug Product Specifications
  - Importance of Determining In Vivo Impact
- The Role of Biopharmaceutics
  - BA/BE Studies
  - Dissolution
  - Advantages and Limitations
- The Role of Models in Setting Clinically Relevant specifications
  - Types of Modeling Approaches
    - Dissolution Models
    - IVIVC Models
    - Model Linking CQA-PK/PD
  - Case Studies

What Are Clinically Relevant Specifications (CRS)?

- CRS are those specifications that help to establish consistent in vivo performance as proven by their ability to reject batches with inadequate in vivo performance

Why is Important to Determine the in vivo Impact?

- When linked to meaningful *in vitro* tests, enables:
  - Development of science and risk based specifications

- Consistent safety and efficacy profiles for the marketed product relative to those for the clinical trial formulation

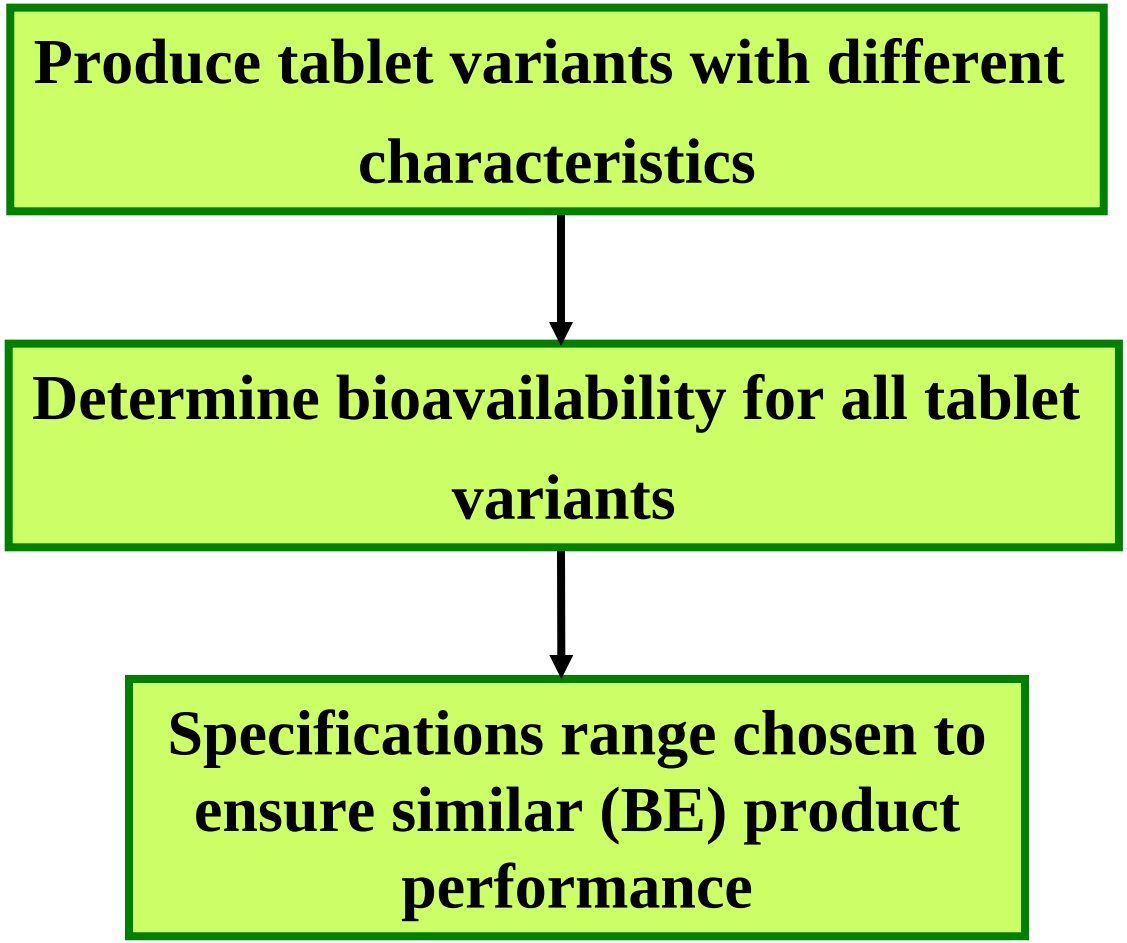
Why is the Use of Biopharmaceutics Relevant?

- These tools are necessary, as it would be impractical to define the impact of each component and manufacturing step through clinical studies

- Plasma drug concentrations are identified as the most successful surrogate for safety and efficacy

An Approach for Setting CRS

- Manufacturing product variants resulting in markedly different plasma concentrations will provide a mechanistic understanding of the critical manufacturing variables

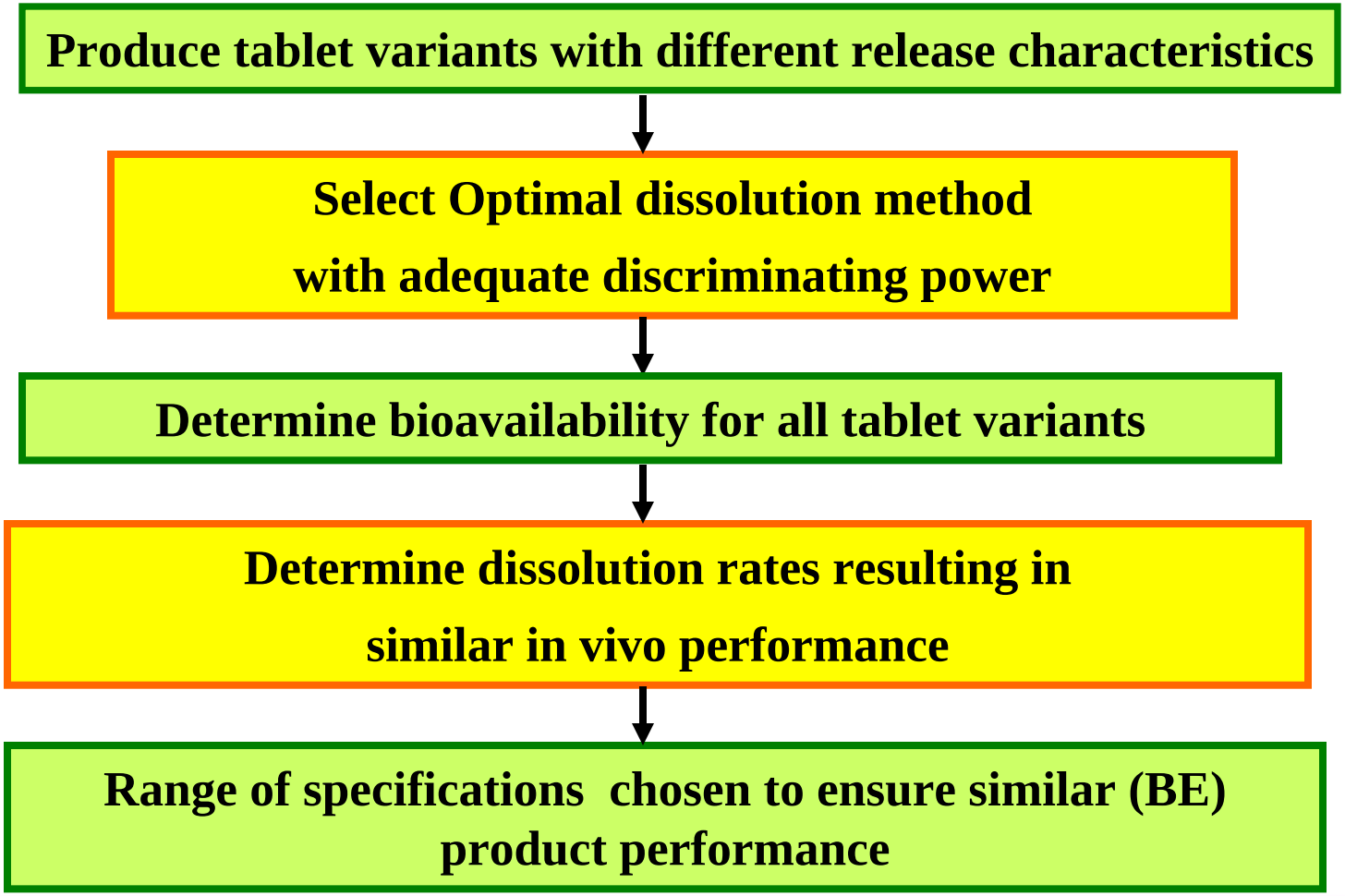


The Relevance of Dissolution

- This tool is necessary, as it would be impractical to define the importance/impact of each component and manufacturing step through PK studies

- Dissolution has been identified as a surrogate for bioavailability
  - Products can be approved based only on the comparability of their dissolution profiles without having to conduct in vivo studies

An Ideal Approach for Setting CRS



What are the Advantages of this Approach?

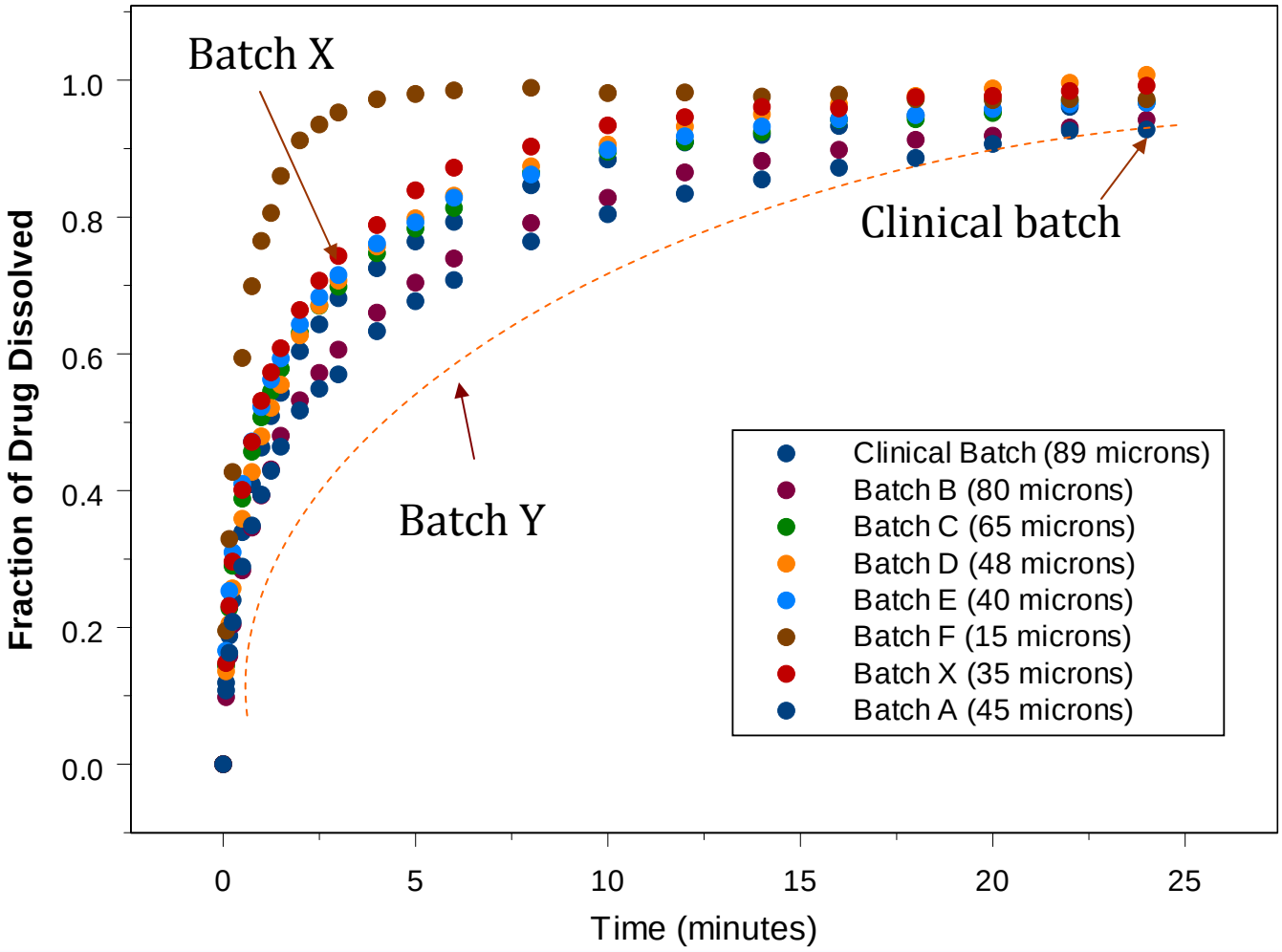
- Clinical performance is always assured within the ranges tested
  - Decisions are based on in vitro and in vivo considerations
- Regulatory flexibility resulting in wider specifications

What Are the Limitations of this Approach?

- Clinical performance can only be assured for the following CMC changes:
  - Those evaluated in the bioequivalence study; or
  - Those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE
  - Those changes which meet F2 statistical testing

Illustration of the Limitation

- Formulations A, B, C, D, E, F and clinical batch were evaluated in a BE
- Batches A through E were BE to clinical Batch
- Batch X (additional CMC change) not part of BE study. However, F2 value is > 50
- F2 value for batch Y is < 50



Do the CMC Changes to Batch Y Have an Impact of the Efficacy and Safety of the Drug?

How Can we Answer this Question?

The Role of Models in Setting Clinically Relevant Specifications

- Validated models can provide the means for predicting/determining the clinical impact of CMC changes without the need for additional in vivo studies

Types of Modeling Approaches Used to Set Clinically Relevant Specifications

- Models linking in vitro dissolution to critical quality attributes (CQAs)
  - Assume the use of a biorelevant dissolution method and dissolution acceptance criteria
- Models linking in vitro dissolution to plasma levels (IVIVC models)
- Models linking CQA to PK/PD end points
  - Assumes the establishment of an in vitro/in vivo correlation

Models Linking In Vitro Dissolution to CQAs

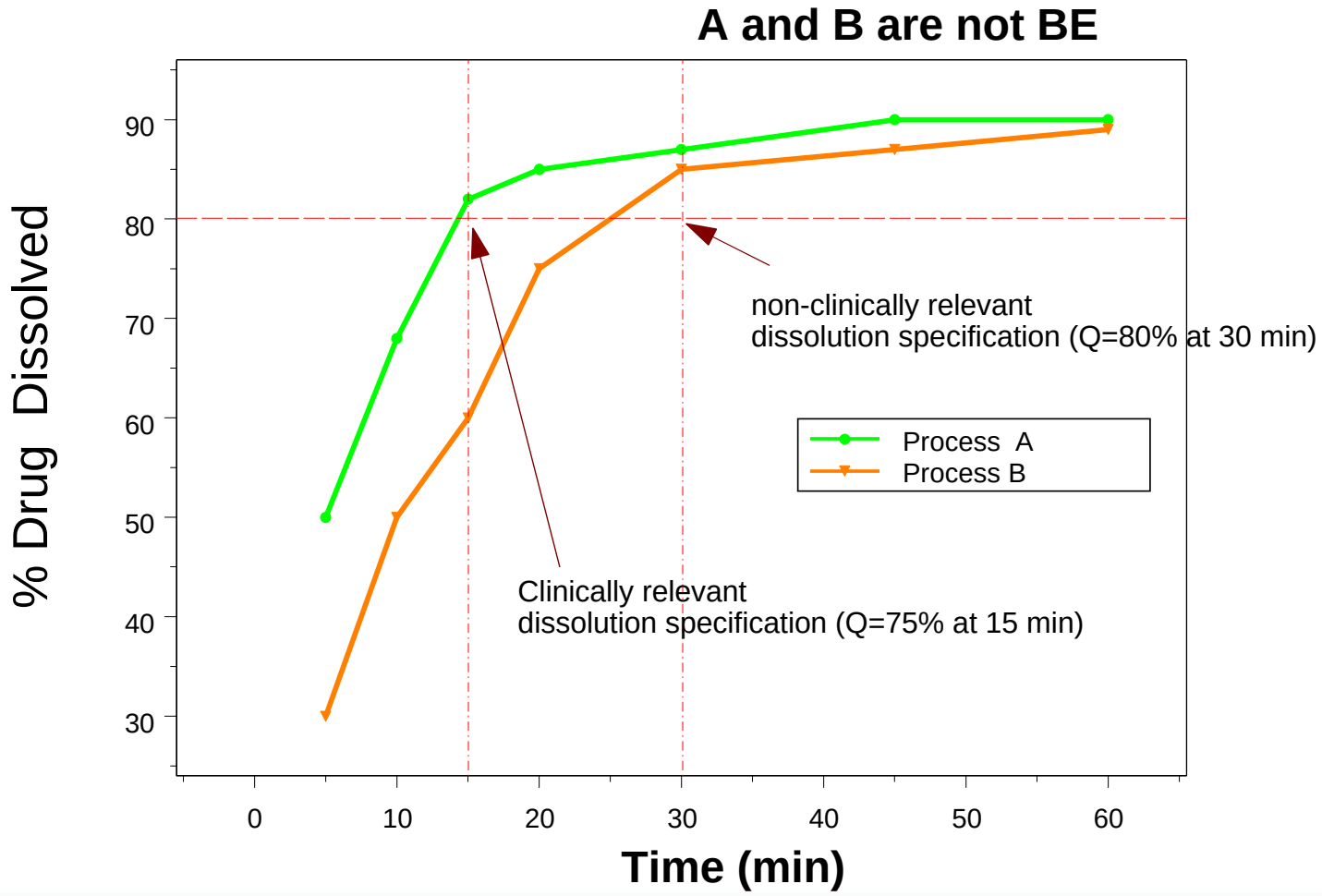
Models Linking In Vitro Dissolution to CQAs

- Dissolution is a CQA
- Assume the use of a biorelevant dissolution method and dissolution acceptance criterion
- Regulatory flexibility limited/determined by the acceptance criterion/similarity F2 testing

Clinically Relevant Dissolution Methods

- Need for a clinically relevant dissolution method
  - The one that has been shown to predict the in vivo impact of changes in manufacturing variables (processes, formulation, etc.)
- The need for a complex dissolution method is not always necessary
- A clinically relevant dissolution specification is possible with the current conventional dissolution methods

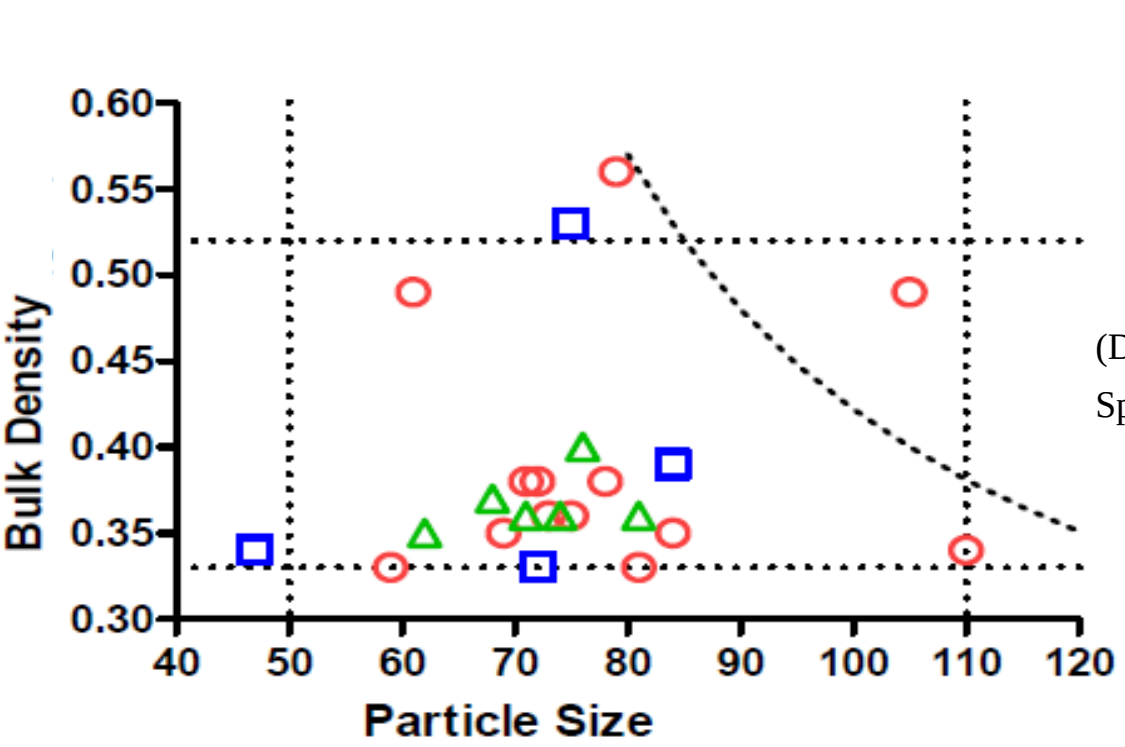
The Importance of Selecting the Appropriate Specifications



Case Study 1

Development of a Dissolution Model to Establish the Ranges for Drug Substance (DS), Particle Size (PS) and Bulk Density (BD)

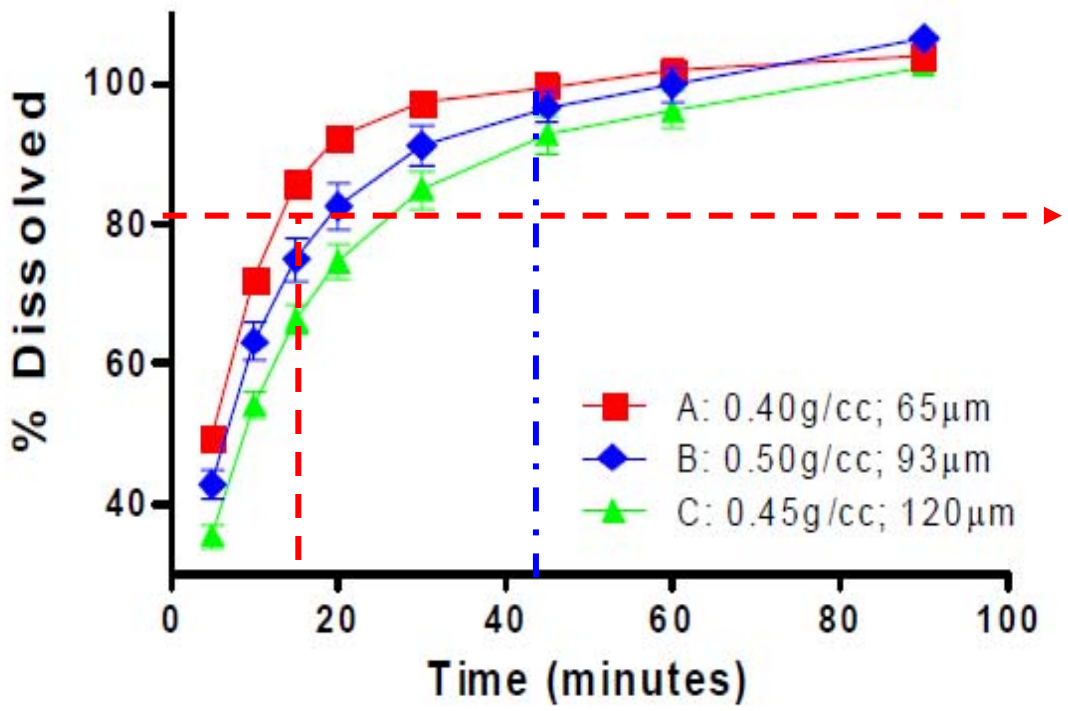
Material Properties of Drug A Used for Experiments



Tablet Production
- DoE
- Development
- GMP

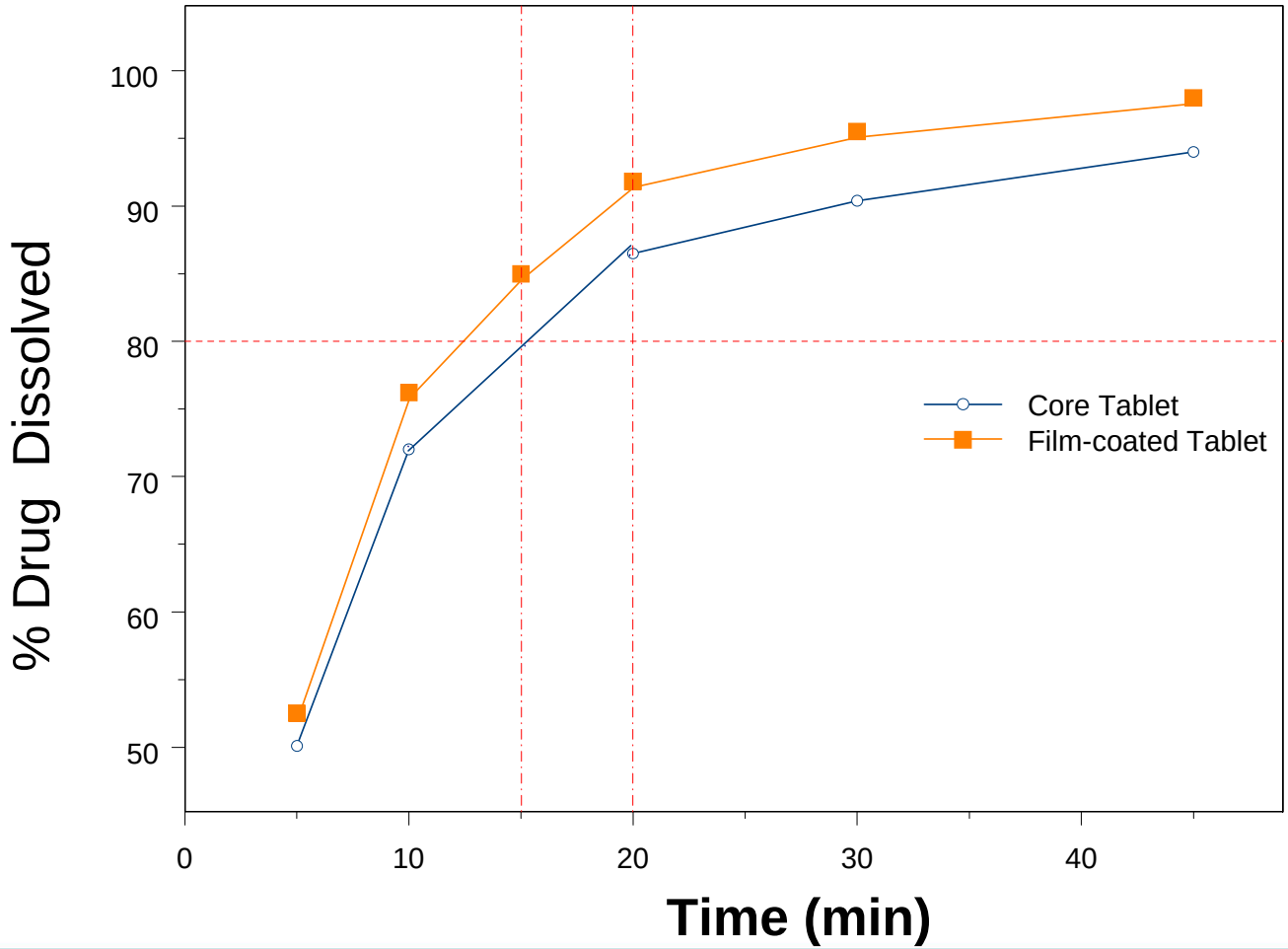
(Dotted Lines Represent Specification Acceptance Limits)

Dissolution Profiles of Tablets with Varying Bulk Density and Particle Size



A (target profile), B (high bulk density), C (large particle size)

Dissolution Profiles of Batches Used in BE



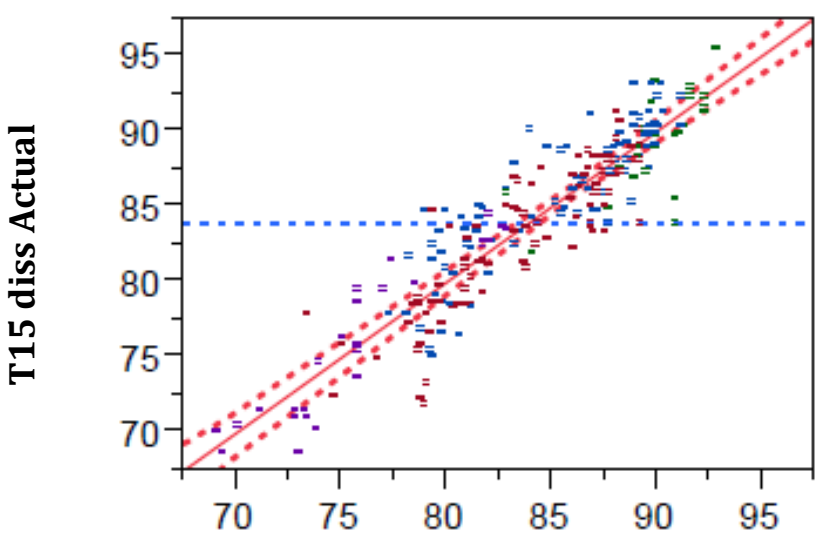
Core Film-coated Tablets are not BE in terms of Cmax

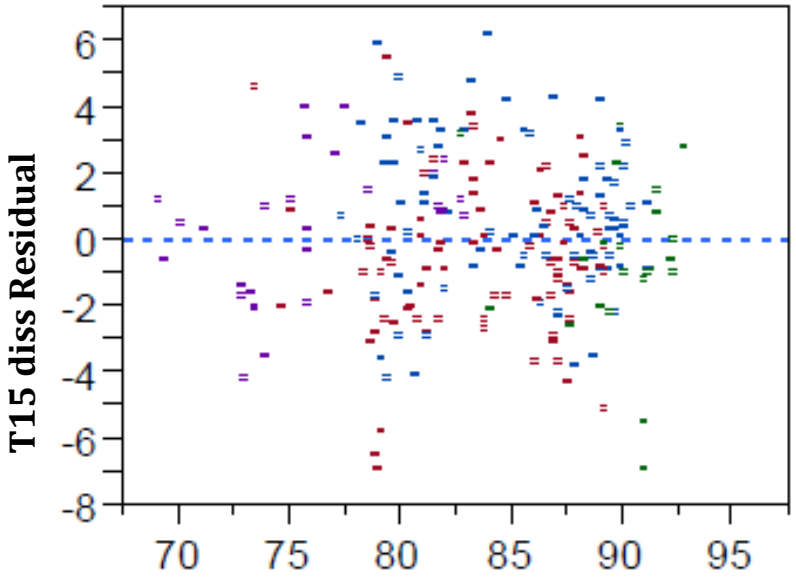
Dissolution Model

- The purpose of the dissolution model was to define the ranges for PS, BD and H to ensure rapid dissolution (Q=80% at 15 min)

- PS, BD and H acceptance limits were justified using the dissolution model and based on data available at the time of NDA submission (DOE and GMP data)

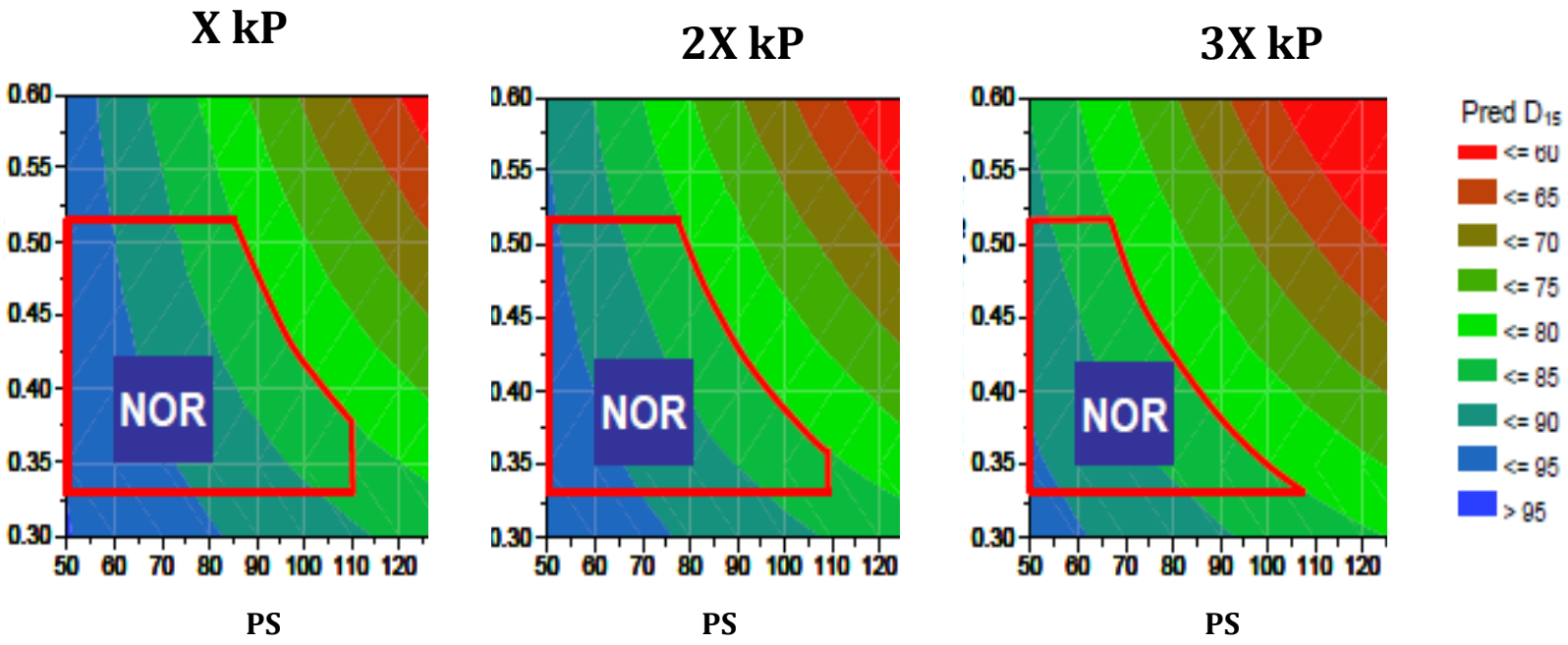
Summary of the Fit of Regression Model





T15 diss Predicted

Design Space for DS Particle Size and Bulk Density at X, 2x, and 3x kP Average Tablet Hardness



PAR for DS particle size and bulk density within red outlined area

NOR for DS particle size and bulk density within the dark blue shaded area

Reported Dissolution Model Qualification Results

- Preliminary attempts on the validation of the model failed
  - The qualification resulted in a positive bias: the mean dissolution for all lots was higher at 15 min, compared to the value predicted based on DS PS/BD and average tablet hardness
    - Did not distinguish between the control strategy verification vs. the continuous process understanding
    - The acceptance criterion was too stringent and not realistic for model qualification

Internal Assessment of the Dissolution Model

- The dissolution model is considered adequate:
  - Internal, cross-validation, and external validation of the model revealed that it is able to predict dissolution at 15 min within the PAR and even outside the PAR with a mean prediction error of less than 6%
  - Applying the principles for internal validation's requirement (mean %PE <10%) stated in the IVIVC guidance, a value of 6% of PE indicates the existence of a predictive model

Lessons Learned

- The development of a clinically relevant (predictive/ discriminating) dissolution method is critical in the setting of clinically relevant specifications
- It is crucial to adopt the right criteria for model selection and validation
  - Proposed criteria for model acceptability that are either too stringent or too wide and not realistic for model qualification
- Amount and type of data needed for model calibration and validation

Models Linking In Vitro Dissolution to Plasma levels (IVIVC models)

IVIVC Models

- Permits the setting of specifications based on targeted clinically relevant plasma concentrations
- Regulatory flexibility resulting in wider specifications
- Most applicable to modified release formulations

Case Study 2

Establishment of an IVIVC Model to Justify DS Particle Size Ranges

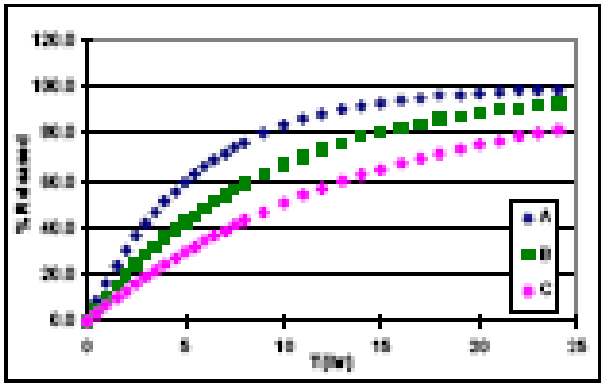
Drug Product Z

- BCS 2 Drug Substance
- Immediate Release Tablet
- Single strength

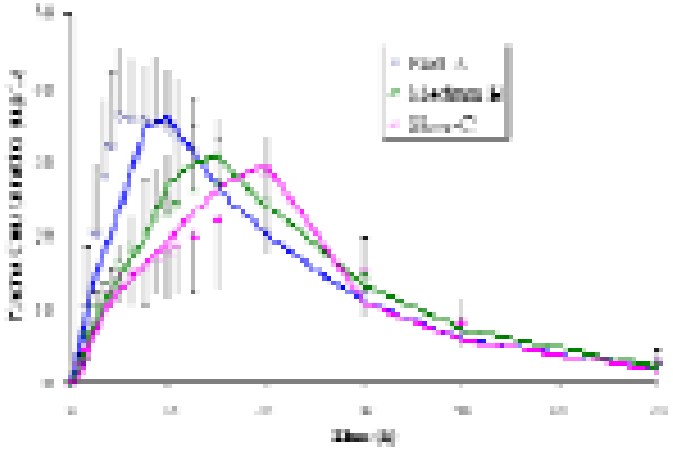
Data Used for the Construction of the Model

- Dedicated PK study to determine the effect of PS on Bioavailability
  - Four batches with different particle sizes
  - Clinical Batch included
  - UIR from IV study
- QC Dissolution Method

Level A IVIVC Model



BA Study



Disposition Function (IV. IR Cp profiles)

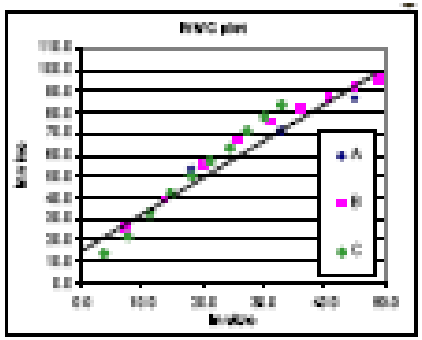
Deconvolution

$C(t) = f(t) * C_d(t)$

Convolution

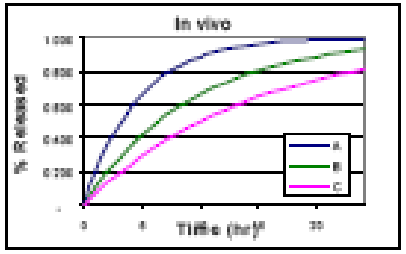
Modeling relationship

IVIVC Model



Validation

Estimated in vivo input



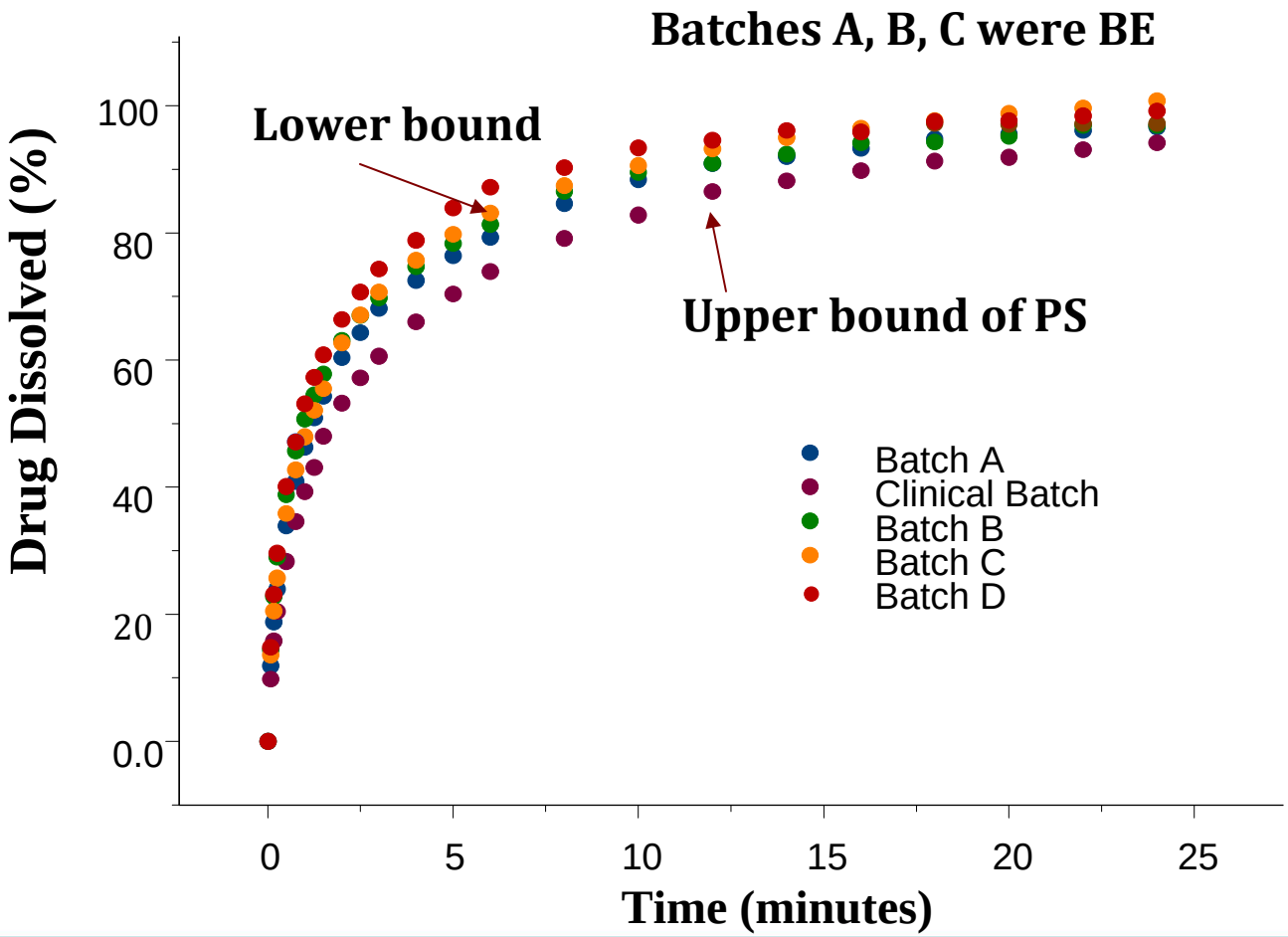
Internal Assessment of the Model

- *The model is not acceptable for the following reasons:*
  - *There is no rank order between dissolution profiles and in vivo exposure (i.e. Cmax) for the batches used in the construction and validation of the IVIVC*
  - *The Tvivo vs. Tvitro plot shows that the profiles of fraction absorbed vs. fraction dissolved may have a different slope indicating the need for different scaling factors among the batches*

Making Sense of the Data

- Setting clinical relevant PS specifications can still be performed
  - The dedicated PK study provided enough information to determine which dissolution rates result in similar in vivo performance

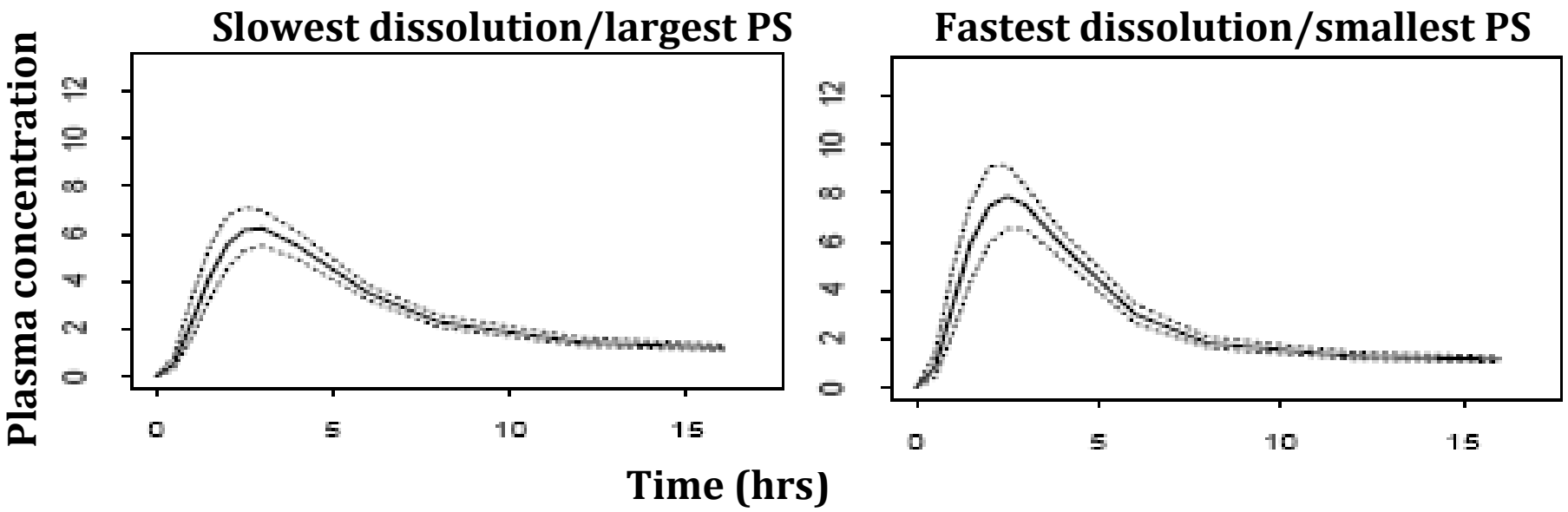
Setting Clinically Relevant PS Ranges



Making the Most Use of the Data

- In addition of the IVIVC development, a Pop-PK analysis was performed to estimate the contribution of the dissolution rate to the overall increase in Cmax
- The absorption phase was described with a transit compartment model related to a two compartment model
- The simulations of the Pop-PK analysis estimated the effect of the single covariate only (i.e. % dissolved at 10 min) on Cmax
- The obtained population PK model was also used to simulate steady-state for drug Z based on the contribution of in vitro dissolution to the PK only

Single Dose Simulated PK of Drug Z with in Vitro Fractions Dissolved at 10 Minutes



- The Pop PK model predicted a 26% difference in median Cmax values between the minimum and maximum DS10 values (outer ranges of batches evaluated) following single dose administration

Lessons Learned

- Clinical relevancy of the specifications for material attributes/process parameters can still be determined in the absence of an IVIVC model
  - Clinical relevancy can only be assured for those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE

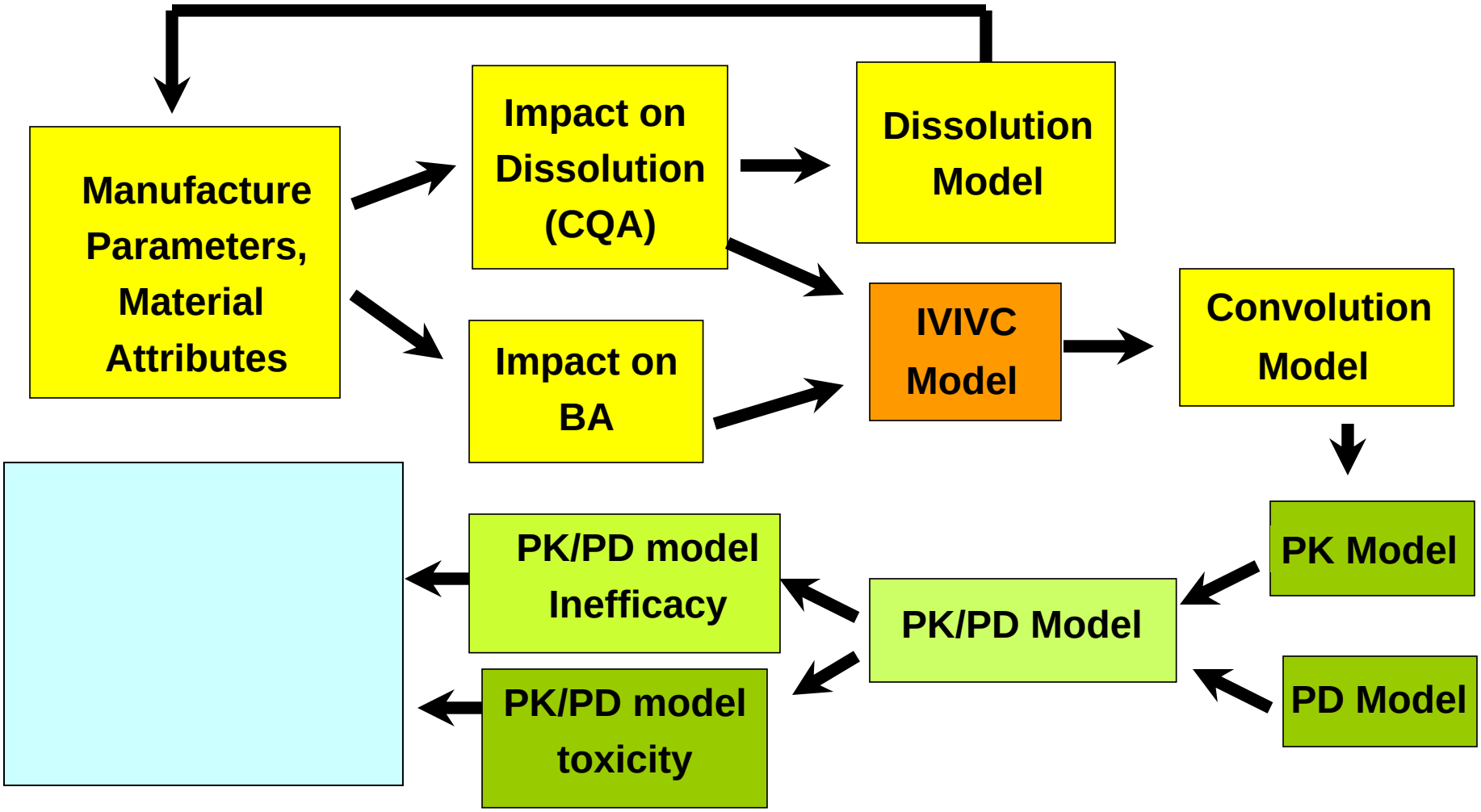
- IVIVC development should be planned a priori instead of being a post-hoc event
  - Ensures the use of robust/appropriate analysis of the data
  - Increases the outcome of a successful correlation

Models Linking CQA to Pharmacodynamic/Clinical End Points

Models Linking CQA-PK/PD

- Permits setting specifications based on targeted clinical outcomes
- Regulatory flexibility resulting in wider specifications
- Need for an acceptable IVIVC
- Dissolution is a CQA

Models Linking CQA-PK/PD



Summary

- Setting clinically relevant specifications starts with the development of a clinically relevant (predictive) dissolution method and dissolution acceptance criterion
  - Ability to detect which CMC changes that affect in vivo performance

- Clinically relevant product specifications
  - Establishment of a relationship between dissolution and BA
    - Clinical relevancy can only be assured for manufacturing changes resulting in dissolution profiles that fall within the extremes of dissolution profiles for batches that were BE
  - Dissolution Models
    - Regulatory flexibility limited/determined by the acceptance criterion/F2 testing

Summary, cont.

- IVIVC models
  - Most desirable approach
    - Regulatory flexibility resulting in wider specifications
- Models linking CQA-PK/PD models
  - Needs the establishment of an acceptable IVIVC

- The ultimate goal is to assure consistent safety and efficacy performance for the marketed product relative to those for the clinical trial formulation

Acknowledgements

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